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ABSTRACT

Introduction: Cerebellar circuits are hypothesized to play a central role in the pathogenesis of essential tremor. Rhythmic finger tapping is known to strongly engage the cerebellar motor circuitry. We characterize cerebellar and, more specifically, dentate nucleus function, and neural correlates of cerebellar output in essential tremor during rhythmic finger tapping employing functional MRI.
Methods: Thirty-one propranolol-sensitive essential tremor patients with upper limb tremor and 29 healthy controls were measured. T2*-weighted EPI sequences were acquired. The task consisted of alternating rest and finger tapping blocks. A whole-brain and region-of-interest analysis was performed, the latter focusing on the cerebellar cortex, dentate nucleus and inferior olive nucleus. Activations were also related to tremor severity.
Results: In patients, dentate activation correlated positively with tremor severity as measured by the tremor rating scale part A. Patients had reduced activation in widespread cerebellar cortical regions, and additionally in the inferior olive nucleus, and parietal and frontal cortex, compared to controls.
Conclusion: The increase in dentate activation with tremor severity supports involvement of the dentate nucleus in essential tremor. Cortical and cerebellar changes during a motor timing task in essential tremor might point to widespread changes in cerebellar output in essential tremor.

1. Introduction

ET (essential tremor) is one of the most common neurological disorders characterized by a progressive postural or kinetic tremor [1]. ET is considered to be a heterogeneous disorder, since patients may differ with regards to the presence of head tremor, their family history and response to medication [2]. In ET, functional, metabolic and structural abnormalities in the cerebellum and brainstem have been identified by different imaging techniques and pathology studies [3,4] (see Ref. [5] for a review of imaging studies). The dentate nucleus is the sole source of output from the cerebellar network. GABAergic Purkinje cell axons are the main afferents to the dentate nucleus [6]. A decrease of GABA receptors in the dentate nucleus has been linked to essential tremor [3]. In addition, DTI changes in the dentate nucleus related to increased disease duration have been observed [7]. Functional changes in the dentate nucleus related to tremor severity have not been investigated previously. The first aim of our study was to objectify whether functional changes in the dentate nucleus are present, related to tremor severity.

As mentioned previously, functional cerebellar changes are postulated to occur in ET. Tremor often diminishes upon alcohol consumption and gait disturbances have been reported [8,9]. Furthermore, impaired eye blink conditioning points to functional cerebellar changes in ET [10]. There is evidence for structural changes in cerebellar outflow structures in ET [7,11,12]. In contrast,

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little is known concerning functional changes in the cerebellum. ET patients show timing impairments, which can partially be reversed by repetitive transcranial magnetic stimulation over the cerebellum [13,14]. This suggests an impairment of cerebellar function, with involvement of the cerebello-thalamo-cortical and olivocerebellar circuitry. Our second aim was to investigate functional changes within these circuits, related to changes during rhythmic motor task performance in ET. We hypothesize that activations are decreased in cerebellar output regions.

We employed a finger tapping task that is known to strongly engage the cerebellar motor circuitry in a selected homogeneous group of ET patients with a positive response to propranolol treatment and disease onset before the age of 65.

2. Materials and methods

2.1. Participants

Thirty-one propranolol-sensitive ET patients with upper limb tremor (21 male; 55.4 ± 15.8 years, average ± standard deviation) and 29 healthy controls (20 male; 52.6 ± 16.1 years) were measured in two medical centers (Amsterdam and Groningen, the Netherlands). Age and gender did not differ between groups ($p > 0.05$). All participants were right-handed according to the Annett handedness questionnaire [esupp ref 1], were aged 18 years or older and gave written informed consent before participation. Patients fulfilled the criteria for essential tremor defined by the Tremor Investigation Group [esupp ref 2], with a positive effect of propranolol on tremor and no use of other tremor medication. They were willing to temporarily withdraw from propranolol for the MRI scan, had experienced disease-onset before the age of 65 and had a disease duration greater than 5 years. Patients quit their medication minimally three days before the study, to allow for proper washout of propranolol. Tremor severity was rated by an experienced movement disorders specialist (JD) by means of the TRS (Tremor Rating Scale) [esupp ref3] while patients were off medication. Exclusion criteria for both patients and their healthy age- and gender-matched controls were the presence of (other) neurological disorders, cognitive dysfunction (i.e., Mini-Mental State Examination < 26) and incompliance with the MR scanner protocol. For full clinical characteristics see Table 1. The study was approved by the local medical–ethical boards and was performed in accordance with the Declaration of Helsinki (2008).

2.2. Task paradigm

Participants had to repeatedly tap their right thumb upon their right index finger, middle finger, ring finger and little finger, and then again in the reverse order. Before scanning, subjects were carefully instructed and practiced the task outside the scanner to ascertain correct task performance. Tapping onset and offset instructions were projected onto a screen, located outside the scanner bore and visible by way of a mirror, to instruct subjects when to perform the task during scanning. Tapping was cued with auditory stimuli, presented at a rate of 2 Hz via headphones, which were present during tapping and rest. The task consisted of 6 epochs of 30 s of finger tapping alternated with epochs of 30 s rest, with 15 s rest at the beginning and end of the task. The total task thus lasted 6 min.

2.3. Data acquisition

BOLD (blood oxygenation level-dependent) functional images were acquired with a 3T-MRI scanner (Intera (Groningen), SENSE 32-channel head receive coil; and Achieva (Amsterdam), SENSE 8-channel head receive coil; Philips, Eindhoven, the Netherlands) using a gradient echoplanar T2*-weighted sequence (echo time: 30 ms; repetition time, 2000 ms; flip angle: 70°; field of view 224 × 224 mm; voxel size 3.5 mm^2). Thirty-nine axial slices covering the entire brain and cerebellum were obtained for a total of 180 volumes. Additionally, a high-resolution anatomical T1 3D TFE image was obtained (echo time: 3.53 ms; repetition time: 9 ms; flip angle: 8°; field of view: 256 × 256 mm; voxel size 1 mm^3, number of slices: 170). Foam padding was used to minimize head motion. Additionally, EMG (electromyography) was recorded concurrently from the lower arm muscles to determine on- and offsets of the task and accurate task performance. EMG recordings and analysis have been described in detail before [esupp ref 4]. Correct task performance was assessed by visual inspection during scanning and by identifying whether a 2 Hz peak was present in the EMG power spectrum.

Table 1
Clinical characteristics.

	Age	Sex	Disease duration	Age at onset	Family history	TRS score A	TRS score B	Head tremor	Propranolol dosage (mg)
1	21	M	11	10	+	0	8	−	40
2	22	M	10	12	+	1	5	−	20
3	27	M	27	0	+	4	12	−	160
4	30	F	15	15	+	0	7	−	20
5	35	M	28	7	+	3	8	−	80
6	41	M	6	35	+	0	4	−	80
7	46	M	41	5	+	3	7	−	80
8	47	M	6	41	+	5	10	−	160
9	47	M	32	15	+	3	7	−	40
10	48	F	38	10	+	10	17	+	120
11	53	F	25	28	+	6	16	+	30
12	53	M	37	16	+	4	11	−	50
13	53	M	38	15	+	1	5	−	20
14	54	F	18	36	+	1	9	+	80
15	57	M	42	15	+	8	9	−	160
16	57	M	39	18	+	4	12	−	10
17	57	F	35	22	+	6	11	+	10
18	63	M	45	18	+	4	6	−	80
19	63	M	20	43	+	4	7	−	40
20	63	F	24	39	+	8	13	−	80
21	64	F	10	54	+	7	15	+	20
22	64	M	52	12	+	2	5	−	20
23	66	M	6	60	+	1	10	+	160
24	68	M	7	61	+	4	10	+	40
25	70	F	40	30	+	2	7	−	80
26	71	M	10	61	+	4	14	+	10
27	72	M	62	10	+	11	20	+	360
28	73	F	55	18	+	7	14	+	80
29	74	M	24	50	+	3	20	−	80
30	77	M	15	62	+	4	11	−	80
31	80	F	20	60	+	8	21	−	80

Clinical characteristics of the patient group. All patients were propranolol sensitive. Item A on the TRS (Tremor Rating Scale) represents tremor severity of the arms in rest, posture and during action. Item B of the TRS represents tremor severity during writing, spiral drawing and specific tasks. TRS scores were assessed while off medication. M = male, F = female, + = present, − = absent.

2.4. Data pre-processing and analysis

Pre-processing and data analysis was carried out using SPM8 (Wellcome Trust Centre of Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks, Sherborn, MA). EPI images were spatially realigned using a least squares approach and a six parameter (rigid body) spatial transformation to the first EPI image and coregistered to the T1-weighted anatomical image. For the whole brain analysis, images were spatially normalized using DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) [esupp ref 5]. For the infratentorial structures, images were spatially normalized using the SUIT (spatially unbiased infra-tentorial template) [esupp ref 6] procedure including hand-drawn masks of the dentate nucleus on the mean EPI images [15]. The SUIT normalization procedure is known to have more accurate inter-subject alignment of cerebellar structures. Images were resampled at 2 mm^3 and smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel. For the dentate nucleus analysis, images were resampled at 1 mm^3 and smoothed with a 4 mm full-width at half-maximum isotropic Gaussian kernel.

The actual on- and offsets of the task, as detected by EMG, were used to temporally correct the task regressor [esupp ref 4], which was subsequently convolved with the canonical hemodynamic response function. Movement effects were modeled by including linear and quadratic effects, and spin-history effects, of the 6 rigid-body motion parameters and were added as nuisance covariates in the design matrix of a GLM (General Linear Model), giving a total of 24 regressors in addition to those describing the task [esupp ref 7]. Intensity changes attributable to movements of the arm through the magnetic field were accounted for by including the time series of the mean signal from the white matter and CSF in the GLM [esupp ref 7]. Serial correlations were modeled as a first order auto regressive (AR(1)) process, and low frequency drifts as a discrete cosine set (128 s cut-off). The parameter "defaults.mask.thresh" in SPM was changed from 0.8 to 0.5 to avoid signal drop-outs within the hypo intense cerebellar nuclei due to high iron-content [15].

2.5. Statistical analyses

For the second-level within group and between group comparisons, nonparametric permutation tests were performed (Statistical non-Parametric Mapping 13b, http://www.sph.umich.edu/ni-stat/SnPM/, [esupp ref 8] 10,000 permutations). Contrasts were built to test for 1) significant within group activations, 2) significant between group differences, and 3) significant correlations of activations with tremor severity (item A on the TRS), disease duration and presence of head tremor in the patient group. Item A on the TRS represents tremor severity of the arms in rest, posture and during action and was used as a surrogate marker to estimate tremor severity during finger tapping. All activations were reported for voxels detected at $P < 0.05$ (FWE corrected). For the between-group analysis, a cluster-wise inference was used ($P < 0.05$ (FWE corrected), cluster-forming threshold $P < 0.001$). SVC (small volume correction) was performed using either the dentate nuclei or the inferior olive nucleus as ROI (region of interest). An ROI near the location of the inferior olive nucleus was drawn, based on the inferior olive location reported in Xu et al. [16](see Supplementary Fig. 1). The dentate mask was separately derived from the Probabilistic Cerebellar Atlas [esupp ref 9]. The probabilistic atlas of the cerebellar cortex and the AAL toolbox were used to define anatomical locations of activations [esupp ref 9, esupp ref 10].

3. Results

3.1. Task performance

All subjects performed the task correctly, as concluded from a visible peak around 2 Hz in the EMG spectrum.

3.2. Within group, tapping task

In both the patient and control groups, activation related to the tapping task was observed in widespread cortical and cerebellar areas, with local maxima in the bilateral primary motor cortex, supplementary motor areas, basal ganglia, thalamus, anterior and posterior cerebellum and parietal regions (Supplementary Figs. 2 & 3).

3.3. Between group, tapping task

The patient group showed reduced activations in widespread regions of the cerebellum, parietal and frontal cortex compared to healthy controls during the finger tapping task (Fig. 1, Table 2). Additionally, reduced activation was observed in the inferior olive nuclei (Fig. 2a, Table 2) and left dentate nucleus (Table 2). The patient group showed no significant increase in activation in any of the contrasts.

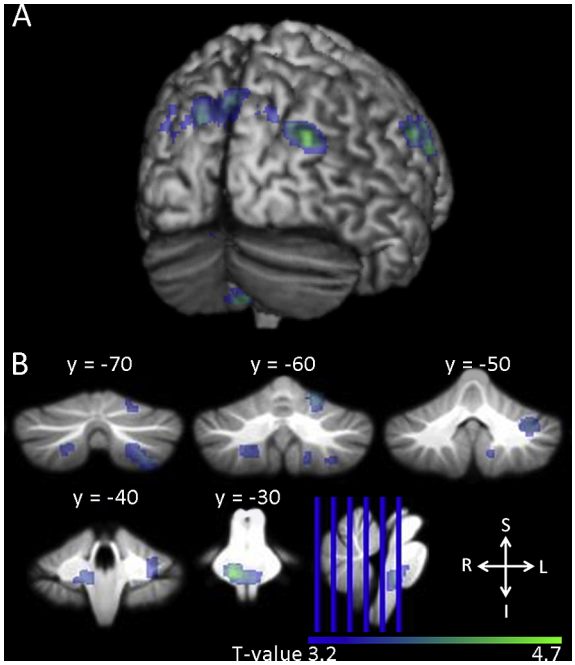

Fig. 1. Between group differences. Tapping task, between group differences in whole brain (A) and cerebellar (B) analyses. Results are projected on the ch2-template (whole brain) or SUIT-template (cerebellum). Cluster-wise inference is used ($p < 0.05$ FWE corrected, cluster-defining threshold of $p < 0.001$).

3.4. Tremor related activation

Tremor score (part A of the TRS) correlated positively with activation in both dentate nuclei (Table 2, Fig. 2b). Tremor score (part A of the TRS) did not correlate with activations in the whole brain, cerebellum or inferior olive nuclei. Disease duration and head tremor showed no relationship with activation in the dentate nuclei. Tremor score, disease duration and head tremor did not correlate with activations in the whole brain, cerebellum or inferior olive nuclei.

4. Discussion

This is the first report of dentate nucleus activation correlating positively with tremor severity in patients with ET. Furthermore, we show reduced activations in widespread cerebellar and cortical regions and the inferior olive nucleus, during a motor timing task in patients with ET compared to healthy participants. This suggests that dysfunction of the cerebellar cortex in ET might lead to altered dentate nucleus functioning, subsequently causing functional changes in areas outside the cerebellum.

4.1. Increasing tremor severity is associated with increased dentate nuclei activation

The positive correlation between activations in the dentate nucleus and tremor severity can be explained in multiple ways. Increased 11C-flunazenil binding to GABA-receptors [17] and a decrease in the number of GABA receptors in the dentate nucleus [3], in combination with our findings, might indicate a primary role

Table 2
Local maxima of finger tapping activity in healthy controls > ET patients (upper part) and local maxima of finger tapping activity correlated with tremor severity in ET patients (lower part).

Region	Hemisphere	*t* value	$P_{FWE\text{-}corr}$	Cluster size	x,y,z in mm		
Healthy controls > ET							
Inferior parietal lobule	Right	4.77	0.0038	1395	34	−66	22
Cuneal cortex	Right	4.51			26	−68	20
Inferior parietal lobule	Right	4.24			36	−76	28
Premotor cortex BA6	Right	4.57	0.0481	242	64	4	22
Primary sensory cortex BA 3b	Right	4.36			62	−10	28
Premotor cortex BA6	Right	4.20			62	4	32
Middle cerebellar peduncle	Right	4.79	0.0061	447	10	−30	−36
Cerebellum lobule VI	Left	4.25	0.0106	291	−20	−60	−16
	Left	3.38			−20	−72	−22
Cerebellum lobule VIIb	Left	4.14	0.0076	361	−30	−70	−54
Cerebellum lobule IX	Left	3.59			−10	−56	−50
Cerebellum lobule VIIIb	Left	3.44			−14	−62	−54
Cerebellum lobule VI	Left	3.86	0.0157	219	−32	−50	−32
Cerebellum lobule VIIIa	Right	3.83	0.0280	141	22	−66	−48
Inferior olive nuclei	Left/Right	2.91	0.0095	15	2	−34	−48
Dentate nucleus	Left	3.35	0.0365	23	−14	−63	−40
Dentate nucleus	Left	3.28	0.0433	5	−12	−60	−34
Finger tapping activity correlated with tremor severity in ET patients							
Dentate nucleus	Left	4.36	0.0087	57	−18	−56	−31
Dentate nucleus	Right	3.73	0.0325	3	18	−50	−38

Upper part: stereotactic coordinates of the local maxima of clusters showing reduced activations in ET compared to healthy controls ($p > 0.05$, FWE corrected, cluster-defining threshold of $p < 0.001$). Cluster size is given in number of voxels. MNI stereotactic coordinates for cortical regions, SUIT coordinates for infratentorial regions. Lower part: SUIT coordinates of the areas within the dentate nucleus for which brain activation during finger tapping correlates with tremor severity ($p > 0.05$, FWE corrected).

of the dentate nucleus in the generation of ET. However, dysfunction of the cerebellar cortex could also lead to disinhibition of the dentate nucleus [18]. Purkinje cells exert a strong inhibitory effect on the cerebellar nuclei, which constitute the exclusive output channels of the cerebellar circuitry. Although still under debate, a loss of Purkinje cells has been attributed to ET and this could also lead to disinhibition of the dentate nuclei indirectly [18]. We employed a motor task paradigm, and therefore observed activations of the dentate nuclei should be interpreted within this framework. The activations in the dentate nuclei, located in the dorsolateral part, correspond to regions previously found to be active during finger movements [19]. In our data, functional changes in the dentate nuclei related to tremor severity are only observed in the presumed motor areas of the dentate nucleus, and not in more widespread parts. In this study, only the motor network was actively engaged. It is therefore likely that our study was most sensitive to detect changes related to tremor severity in motor areas of the dentate nucleus. An alternative explanation could be that higher activations in the dentate nuclei are observed due to increasing tapping difficulties associated with increasing tremor severity. Although this cannot be excluded, we would expect to find more functional changes throughout the motor network, and not an isolated increase in dentate nucleus activations. Even at an uncorrected significance threshold of $p < 0.001$ for the whole brain analysis, solely activations in the dentate nuclei are observed related to tremor severity. With resting-state fMRI, one could try to assess whether there is a general dysfunction of the dentate nucleus with increasing tremor severity, or if only the motor areas of the dentate nucleus are involved in essential tremor.

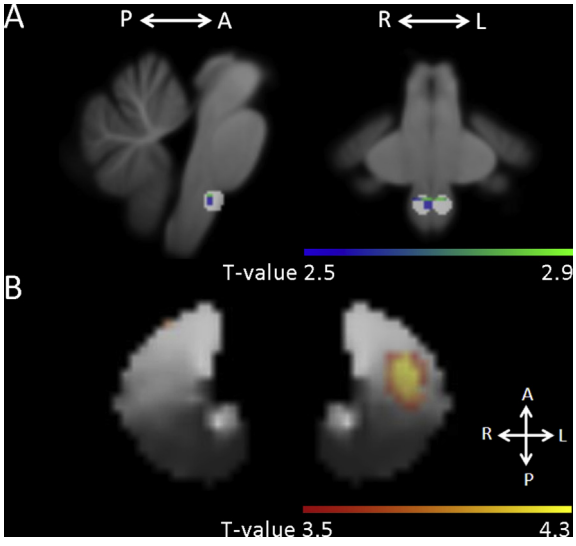

Fig. 2. Inferior olive nucleus and dentate nucleus. A. Tapping task, between group differences within the inferior olive nucleus mask projected on the SUIT template (small volume correction, $p < 0.05$ FWE corrected). B. Dentate nucleus activation correlated with increasing tremor score (TRS part A) in ET projected on the dentate nucleus mask (small volume correction, $p < 0.05$ FWE corrected).

4.2. Cerebellar cortex and inferior olive dysfunction

The reduction in BOLD activations during tapping in widespread areas of the cerebellar cortex and middle cerebellar peduncle suggests dysfunction of these regions in ET. GABAergic neurotransmission dysfunction within the cerebellum has been observed before, increasing with tremor severity [20], together with other functional and structural changes within the cerebellum [21,22]. Additionally, a modest decrease in the number of Purkinje cells and swollen Purkinje cell axons, known as torpedoes, have been reported in ET patients [4]. Although these findings are still debated, they could serve as a possible explanation for our results. Purkinje cells lead to the dentate nuclei, and form the sole output channel from the cerebellar cortex. In this manner, Purkinje cells strongly regulate the intrinsic activity of the dentate nucleus [6]. Whether cerebellar pathology is secondary to changes in the dentate nucleus, or vice versa, remains controversial. Previously observed difficulties in ET related to motor timing could also be regarded as consequences of cerebellar and inferior olive nucleus dysfunction [13,14]. ET patients show decreased ability to synchronize

repetitive movements to extrinsic timing cues [13]. They also show timing impairments which can partially be reversed by repetitive transcranial magnetic stimulation over the lateral cerebellum [14]. Decreased cerebellar activity in ET was mainly located in the left hemisphere of the posterior cerebellum, including lobules VI, VII, VIII and IX. Activity in the bilateral posterior cerebellum has been linked to temporal aspects of motor tasks [23–25]. A decrease in cerebellar activations has previously been described during a similar finger tapping task in patients with spinocerebellar ataxia [26]. The authors hypothesize that the decrease in activation is a consequence of limited functional reorganization in spinocerebellar ataxia. Similarly, one would expect that if timing impairments in ET are associated with a dysfunctional cerebellar cortex, a decrease of 'healthy' cerebellar motor activity within regions associated with temporal aspects of movements would be observed.

In the inferior olive nucleus a decrease in activation in ET patients during tapping was seen. It is notoriously difficult to study the activation of small structures in the medulla with functional imaging. This is the first evidence of functional MRI abnormalities in the inferior olive nucleus in ET, in vivo. Previously, increased glucose metabolism of the medulla has been observed in ET patients [27]. We suggest that the decrease in activation in the region of the inferior olive nucleus indicates dysfunction of this nucleus during rhythmic motor timing. This dysfunction can be secondary to pathology in the cerebellar cortex. In a recent post-mortem study, no structural differences were found in the inferior olive nucleus of ET patients compared to controls [28]. Another possible explanation for functional changes in the inferior olive nucleus could be differences in proprioceptive feedback due to tremor. Our findings indicate a widespread involvement of the olivocerebellar system rather than solely the cerebellum in ET. Whether the origin of tremor lies in the dentate nuclei, the cerebellar cortex, or multiple regions entraining each other, remains controversial and cannot be deduced from our results.

In our study, cortical areas including the parietal cortex showed decreased activation during rhythmic finger tapping in ET. These regions are possibly functionally linked to non-motor regions and have been associated previously with the frontoparietal attention network [29]. Additionally, there was decreased activation in ET compared to controls in the ventral part of the dentate nucleus, which is not part of the motor network either [15]. Changes might therefore also be caused by increased attentional and proprioceptive demands necessary to perform the task in tremor patients.

4.3. Methodological considerations

One possible limitation of our study is that we did not include more specific properties of task performance in our design, like touch duration and inter-tapping intervals. Due to the nature of the complex finger tapping task, with low muscle activations involving multiple finger muscles, combined with the low signal-to-noise ratio of the surface EMG, measured in a strong magnetic field, quantifying task performance in terms of more specific characteristics was not possible. Likewise, separating tapping-related from tremor-related activity was not possible using the surface EMG. However, all subjects were visually monitored during scanning and a 2 Hz peak was objectified in the EMG signal of all subjects during the task. Since we chose a short TR of 2 s and scanned the whole brain including the cerebellum, the voxel size was rather large for localizing activation in small regions, especially in the inferior olive nucleus. However, the mask was placed in an area where previous fMRI studies have localized the inferior olive nucleus [16]. Given the widespread decrease in activation in ET within this mask, at least including the inferior olive nucleus, we consider this difference to be reliable, and not due to partial volume effects. Finally, it has been suggested that patients with and without head tremor represent distinct subtypes of ET [30]. Due to the relatively small number of patients with head tremor included in our study (10 patients with head tremor vs. 21 patients without head tremor), a subgroup analysis for this group was not performed.

In conclusion, we report functional changes during motor timing in patients with ET. Our data suggest that dysfunction of the cerebellar cortex might lead to altered activation in the dentate nucleus and inferior olive nucleus and subsequently to functional changes in areas also outside the cerebellum.

Full financial disclosures

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.02.003.

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